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Use of CO_2-derived variables in critically ill patients

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Abstract

A fundamental objective of hemodynamic resuscitation is to reverse tissue hypoperfusion and prevent progression to multiorgan failure and death. Conventional tools such as clinical examination, lactate levels, and central or mixed venous oxygen saturation ($ScvO_2$ and SvO_2, respectively) have intrinsic limitations. These drawbacks can be mitigated by incorporating additional markers of tissue hypoperfusion and altered tissue metabolism, such as carbon dioxide (CO_2)-derived variables, into other multimodal macro and micro hemodynamic monitoring. Specifically, the mixed or central venous-to-arterial difference in partial pressure of CO_2 ($Pv\text{-}aCO_2$ or $Pcv\text{-}aCO_2$) reflects the adequacy of blood flow to transport CO_2 from peripheral tissues to the lungs for its elimination. Consequently, $Pv\text{-}aCO_2$ serves as a reliable marker for assessing the adequacy of blood flow relative to CO_2 production. Importantly, unlike SvO_2 and $ScvO_2$, $Pv\text{-}aCO_2$ remains informative even when oxygen extraction is impaired, as commonly occurs in septic conditions. However, $Pv\text{-}aCO_2$ and $Pcv\text{-}aCO_2$ in isolation are not direct markers of anaerobic metabolism, as these can also be influenced by oxygen consumption rates. Conversely, the ratio between $Pv\text{-}aCO_2$ (or $Pcv\text{-}aCO_2$) and the arteriovenous oxygen content difference may provide a more reliable indication of ongoing anaerobic metabolism. This review discusses the physiological foundations, prognostic significance, clinical implications, and potential applications of CO_2-derived parameters in patient management.

Keywords Venous-to-arterial carbon dioxide tension difference, Carbon dioxide production, Oxygen supply dependency, Tissue hypoperfusion, Tissue hypoxia, Anaerobic metabolism, Oxygen consumption, Haldane effect, PCO_2:CCO_2 dissociation curve, venous oxygen saturation

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Background

Early recognition of tissue hypoperfusion and its reversion are key aspects to limiting the progression of shock and multiorgan dysfunction [1, 2]. For years, shock resuscitation has focused on increasing macro hemodynamics, aiming at reversing the imbalance between oxygen demand and supply to the tissues. Early goal-directed hemodynamic optimization targeting central venous oxygen saturation ($ScvO_2$) was initially associated with a significant reduction of mortality in septic shock [3], but subsequent multicenter randomized trials failed to demonstrate some clinical benefit [4], since $ScvO_2$ is often normal or near normal in approximately two-thirds of septic patients on ICU admission [4, 5], achieving normal macro hemodynamics and/or global oxygen-derived parameters does not necessarily exclude the presence or persistence of tissue hypoxia.

Other markers, such as blood lactate concentration, have been demonstrated to be useful in detecting more severe cases and in guiding resuscitation during shock states [6–8]. Indeed, lactate-guided therapy significantly reduced hospital mortality in critically ill patients when adjusting for predefined risk factors [9]. In survivors, lactate levels almost invariably return to normal, and lactate kinetics have consistently been associated with morbidity and mortality across diverse clinical contexts [10]. However, blood lactate concentration may increase for many reasons unrelated to anaerobic metabolism [11, 12]. In addition, its dynamics is too slow for both an increase during shock progression and a decrease during the resuscitation phase [13]. Furthermore, blood lactate concentration relies on the balance between lactate generation and its reuptake by some tissues such as the liver and kidneys. Altogether, these limitations make lactate an imperfect marker of tissue anaerobic metabolism, tissue hypoperfusion, and a standalone guide for resuscitation.

In this context, using other resuscitation markers, such as carbon dioxide (CO_2)-derived parameters, could provide additional information about macro and micro hemodynamics even in the presence of apparently corrected oxygen-derived variables and lactate levels [14–18]. Remarkably, CO_2-derived parameters evolve more rapidly than resuscitation markers, such as blood lactate and microcirculatory blood flow distribution (evaluated by portable video-microscopy) [13], making CO_2-derived parameters a potential tool for guiding resuscitation.

In this review, we will discuss the physiological principles, prognostic value, clinical significance, and potential clinical applications of CO_2-derived parameters, including the mixed or central venous-to-arterial carbon dioxide difference ($Pv\text{-}aCO_2$ or $Pcv\text{-}aCO_2$) and the mixed or central venous-arterial carbon dioxide to arterial-venous oxygen difference ratios.

Physiology of carbon dioxide

Aerobic CO_2 production

Under aerobic conditions, CO_2 is produced by cells as the terminal metabolic product from substrate oxidation. Total CO_2 production (VCO_2) is directly related to global oxygen consumption (VO_2) by the relation: $VCO_2 = RQ \times VO_2$, where RQ represents the respiratory quotient, which reflects the ratio of moles of CO_2 generated per mole of oxygen consumed. RQ may vary from 0.7 to 1 depending on the predominant energetic substrate consumed. Accordingly, VCO_2 should increase when aerobic metabolism accelerates (i.e., increased tissue oxygen demand) or when carbohydrates are used as the predominant energetic substrate at a given VO_2 [19] (Fig. 1A).

Non-aerobic CO_2 production

During tissue hypoxia, aerobic VCO_2 decreases in proportion to the decline in VO_2. Interestingly, when tissue hypoxia occurs, a portion of CO_2 is non-aerobically generated through the buffering of protons (H^+) by cytosolic and plasmatic bicarbonate (HCO_3^-). Thus, the excess of H^+ is captured by HCO_3^- to form H_2CO_3, which subsequently dissociates into CO_2 and H_2O (Fig. 1B). Nevertheless, the clinical demonstration of non-aerobic CO_2 generation under tissue hypoxia is challenging as the total VCO_2 also decreases [20, 21]. Additionally, the efferent venous blood flow may be sufficient to wash out the total CO_2.

Remarkably, non-aerobic CO_2 generation has been demonstrated in experimental metformin intoxication in which lactic acidosis was accompanied by a non-proportional decrease in VCO_2 with respect to the concomitant VO_2 fall (due to mitochondrial blockage by metformin), resulting in an increase in RQ, even under preserved systemic oxygen delivery (DO_2) [22]. Of note, metformin intoxication induces mitochondrial dysfunction by inhibition of complex I, which is just another form of tissue hypoxia [23, 24]. Additionally, non-aerobic VCO_2 can also result from anaerobic decarboxylation of substrates of intermediate metabolism such as α-ketoglutarate and oxaloacetate, although admittedly, its contribution to the total VCO_2 is relatively small [25].

In summary, non-aerobic VCO_2 might occur during tissue hypoxia, related or not to impairment of tissue perfusion (Fig. 1).

Transport of CO_2 content in blood

The transport of CO_2 in the blood is closely determined by PCO_2 variations, the intracellular and extracellular pH, and the surrounding partial pressure of oxygen (PO_2) [26]. In general, blood carries both CO_2 and its related compounds in five forms:

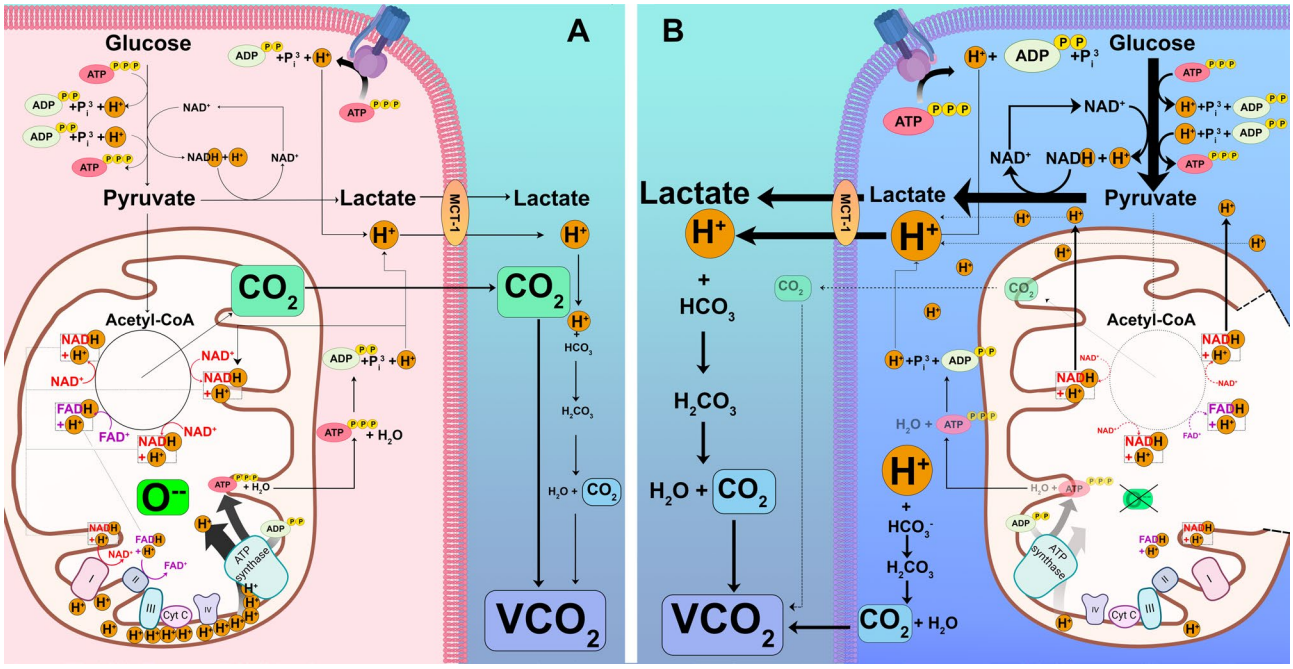

Fig. 1 **A** Aerobic CO_2 generation. Under aerobic conditions, carbon dioxide (CO_2) is produced by the cells as the terminal metabolic product from substrate oxidation. ATP, adenosine triphosphate; ADP, adenosine diphosphate; H^+, hydrogen ion; Complexes I, II, III, CytC, and IV, denote the components of the oxidative phosphorylation chain; MCT-1, monocarboxylate transporter-1; VCO_2, CO_2 production. **B** Non-aerobic CO_2 generation (tissue hypoxia). During tissue hypoxia (right, blue cell), CO_2 is generated by buffering the excess of H^+ not recycled by other energy-generating processes (i.e., Krebs's cycle). Such excess of non-reprocessed H^+ are buffered by cytosolic and plasmatic bicarbonate (HCO_3^-), becoming H_2CO_3 to finally dissociate into CO_2 and H_2O. Thus, non-aerobic CO_2 increase should theoretically contribute to the total VCO_2

1. Dissolved CO_2 $(CO_2)_{DIS}$, which is in equilibrium with the partial pressure of CO_2 (PCO_2) (as stated by Henry's law) and represents ≈ 5% of the total CO_2 content (CCO_2). The actual concentration of $(CO_2)_{DIS}$ depends on the solubility coefficient of CO_2 in plasma, which in turn is influenced by temperature: higher temperatures reduce solubility, while lower temperatures increase it.
2. Carbonic acid (H_2CO_3), due to the reaction between CO_2 and H_2O (catalyzed almost instantaneously by carbonic anhydrase). Nevertheless, at physiological pH, H_2CO_3 instantly dissociates into H^+ and HCO_3^-, whereby H_2CO_3 represents only 1/400th of the total CO_2.
3. Bicarbonate (HCO_3^-), which is generated by the dissociation of H_2CO_3 into H^+ and HCO_3^- by a direct combination of CO_2 and OH^- (also catalyzed by the carbonic anhydrase) and by a combination of carbonate (CO_3^{2-}) and H^+. While H^+ is buffered by hemoglobin, HCO_3^- leaves the red blood cells through the HCO_3^-/chloride anion (Cl^-) exchanger. Thus, HCO_3^- increases in venous blood while Cl^- decreases. In arterial blood, bicarbonate (HCO_3^-) accounts for approximately 90% of the total CO_2 content (i.e., ≈ 435 ml/L in whole blood). Although the absolute HCO_3^- concentration is slightly higher in venous blood due to increased CO_2 loading, the proportion of total CO_2 carried as HCO_3^- is slightly lower. This is because a greater fraction of CO_2 is bound to hemoglobin as carbamino compounds in venous blood, a shift facilitated by the Haldane effect (see below).
4. Carbonate (CO_3^{2-}), which is mainly generated from the dissociation of HCO_3^- into $CO_3^{2-} + H^+$. Nevertheless, $[CO_3^{2-}]$ is not quantitatively important for CO_2 transport as it represents only ≈ 1/1000th of the total HCO_3^- at pH 7.40.
5. Carbamino compounds, which represent CO_2 linked to amino groups (R-NH_2) of proteins, being the carbamino hemoglobin (Hb-NH-COO^-), the most important carbamino compound, accounting for ≈ 5% of the total CCO_2 in blood.

The CO_2 dissociation curve

Although the overall relationship between PCO_2 and total CCO_2 is curvilinear, it remains approximately linear within physiological ranges of PCO_2 and PO_2. Nevertheless, due to the Haldane effect, as hemoglobin gets saturated with O_2, it will carry less CO_2 as a carbamino compound since CO_2 has a greater affinity for reduced than oxygenated hemoglobin [27]. Consequently, when blood enters the pulmonary capillaries and O_2 is transferred to hemoglobin, the CO_2-carrying capacity of hemoglobin decreases, facilitating the pulmonary

excretion of CO_2. The inverse occurs when blood becomes deoxygenated by releasing O_2 to the tissues; then, hemoglobin gains the capacity to transport both extra aerobic and non-aerobic CO_2. Simultaneously, the production of CO_2 and H^+ by tissues promotes the release of O_2 from hemoglobin in the capillaries, a phenomenon known as the Bohr effect. Aerobic mitochondrial metabolism generates CO_2, increasing CCO_2 by ≈4 mL/dL from arterial to mixed venous blood (from 48 to 52 mL/dL), with a small PCO_2 rise (from 40 mmHg in the arterial blood to 46 mmHg in the mixed venous blood) due to the steep CO_2 dissociation curve. Without the Haldane effect, which enhances CO_2 carriage in deoxygenated hemoglobin, venous PCO_2 would rise significantly more for similar CCO_2 increases because less CO_2 could be stored as carbamino compounds and as bicarbonate.

Remarkably, the relationship between PCO_2 and CCO_2 is also influenced by variations in H^+ concentration, temperature, and hematocrit. Thus, blood CCO_2 decreases as pH and HCO_3^- also do, while an increase in temperature reduces the CO_2 solubility, deviating the CCO_2:PCO_2 relationship downwards (Fig. 2). Similarly, an increase in hematocrit reduces the plasma space and increases pH, which ultimately reduces the CCO_2 in blood.

The venous-to-arterial carbon dioxide difference (Pv-aCO_2)

Total venous CCO_2 is determined by the mass of CO_2 aerobically and non-aerobically generated in the tissues, and it is influenced by the metabolic rate and the RQ. Usually, CCO_2 is higher on the venous side, thus creating a difference between the venous and arterial CCO_2 (Cv-aCO_2), which, under normal conditions of flow and metabolism, should be equivalent to the venous-to-arterial carbon dioxide pressure difference (Pv-aCO_2) (the gradient of pressures exerted by the dissolved CO_2 between the mixed venous-to-arterial blood). Nevertheless, arterial PCO_2 might exceed venous PCO_2 under hyperoxic apnea, a condition recreated during an apnea test to diagnose brain stem death [28] or during programmed intubation in the anesthesia setting [29], as a consequence of the Haldane effect. Interestingly, such "inversion" of the Pv-aCO_2 is followed by symmetrical venous and arterial pH changes.

Pv-aCO_2 and its relationship with cardiac output

Pv-aCO_2 depends on the total CO_2 production, cardiac output, and the complex relationship between PCO_2 and CCO_2. The Fick equation states that CO_2 excretion, i.e., the equivalent to VCO_2 at a steady state, should equal the product of cardiac output and the venous-to-arterial CCO_2 difference:

$$VCO_2 = cardiac\ output\ x\ (CvCO_2 - CaCO_2).$$

As CCO_2 and PCO_2 depict a relatively linear relationship at usual physiological ranges ($PCO_2 = k$ x CCO_2), PCO_2 could be used as a surrogate of CCO_2 [30, 31], and the Fick equation might be rewritten as:

$$Pv\text{-}aCO_2 = k\ x\ VCO_2/cardiac\ output.$$

where k is a pseudo-linear coefficient assumed to be constant under physiological conditions. Nevertheless, the factor k may increase considerably under severe hypoxia and metabolic acidosis conditions, causing a significant shift in the curvilinear CCO_2:PCO_2 relationship (Fig. 2).

The modified Fick equation shows that Pv-aCO_2 and cardiac output keep an inverse curvilinear relationship.

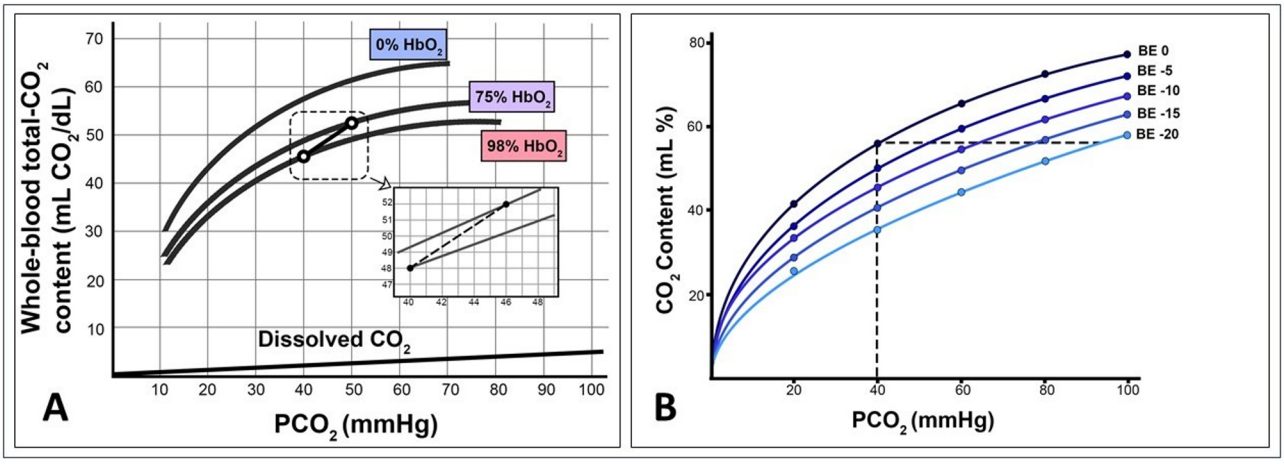

Fig. 2 **A**: Effects of hemoglobin oxygen saturation on the relationship between CO_2 pressures (PCO_2) and contents (CCO_2), i.e., Haldane effect. Curves depict the behavior of CCO_2 at different hemoglobin oxygen saturations (including completely non-oxygenated hemoglobin - SO_2:0% - under "ex vivo" conditions). Hemoglobin-O_2 saturation affects the position of the CO_2 dissociation curve. **B**: Effects of hydrogen ion accumulation on the PCO_2:CCO_2 relationship. Isopleths of base excess (BE) are described as PCO_2 dramatically increasing for similar CCO_2, as long as acidosis (hydrogen ion accumulation) also impairs

Thus, under stable conditions of VO_2 and VCO_2, Pv-aCO_2 will increase progressively in response to reductions in cardiac output due to venous CO_2 stagnation, in which a delayed transit time of red blood cells in the tissues leads to a greater addition of CO_2 per unit of blood flowing through efferent microvessels.

Early observations during cardiac arrest in both animal models and humans revealed a close relationship between no blood flow and venous CO_2 accumulation [31, 32]. Similar results were shown in experimental models of hemorrhage, hypovolemia, and obstructive shock, thus highlighting the importance of blood flow stagnation on venous CO_2 accumulation, which in turn increases Pv-aCO_2 [20, 21, 33, 34].

Can the PCO_2 gaps be used as a marker of tissue hypoxia?

The increase in Pv-aCO_2 was initially interpreted as a marker of tissue hypoxia, as critical DO_2 values seemed to coincide with the point at which venous PCO_2 began to rise in experimental studies [20, 33, 35]. However, these experiments could not distinguish between tissue hypoperfusion and tissue hypoxia. To address this, Vallet et al. [36] compared the effects of hypoxic hypoxia and ischemic hypoxia on the VO_2:DO_2 relationship and regional Pv-aCO_2 in a vascular-isolated canine hindlimb model perfused via a roller pump–membrane oxygenator circuit. To examine the isolated effects of hypoxia or flow, decreases in DO_2 and VO_2 were induced by progressive reductions of the inspired O_2 fraction (FiO_2) but preserving flow (hypoxic hypoxia) and by gradual reductions of the roller pump velocity but maintaining FiO_2 (ischemic hypoxia). Even though both groups experienced similar decreases in DO_2 and VO_2, regional hind limb Pv-aCO_2 remained constant during hypoxic hypoxia, while it increased more than two-fold during ischemic hypoxia, suggesting that blood flow is the major determinant of Pv-aCO_2. Similarly, Nevière et al. [37] showed significant increases in gut mucosal-to-arterial PCO_2 difference (Pmtis-aCO_2) during ischemic hypoxia, while it remained almost constant over a wide range of DO_2 values during hypoxic hypoxia. Interestingly, Pmtis-aCO_2 increased slightly during extreme hypoxic hypoxia, which could indicate some local non-aerobic CO_2 generation. Similar results were observed in experimental hemodilution, in which no increase in Pmtis-aCO_2 was detected under conditions of VO_2:DO_2 dependency due to reduced hemoglobin concentration unless there was a concomitant reduction in cardiac output [38].

Both experimental [36, 37] and clinical [39–41] data suggest that in tissue hypoxia, Pv-aCO_2 can be high or normal, depending on cardiac output. Tissue hypoxia occurring during low flow states increases Pv-aCO_2 due to CO_2 venous stagnation. However, in cases of tissue hypoxia with preserved or increased blood flow, Pv-aCO_2 may be normal or even reduced, as the flow in venous efferent vessels could be sufficient to wash out the CO_2 generated by the tissues, as occurred in hypotensive patients with fulminant hepatic failure and concomitant tissue hypoxia [41]. Consequently, a normal Pv-aCO_2 does not rule out tissue hypoxia or dysoxia.

In summary, Pv-aCO_2 is a useful surrogate of the adequacy of cardiac output and tissue perfusion for a given level of CO_2 production. However, the correlation between variations in cardiac output and Pv-aCO_2 during septic shock is weak [15, 39, 40, 42], suggesting that factors beyond cardiac output also influence Pv-aCO_2 [18].

Tissue-to-arterial CO_2 gaps, Pv-aCO_2, and microcirculatory blood flow alterations

Microcirculatory dysfunction in septic shock is a generalized phenomenon essentially characterized by decreased functional capillary density (FCD) and increased heterogeneity of blood flow, which implies the presence of areas with well-perfused vessels in close vicinity to non-perfused capillaries [43, 44]. Créteur et al. [45] showed a good correlation among sublingual microcirculatory blood flow distribution evaluated by video microscopy, the sublingual-to-arterial PCO_2 difference (Psl-aCO_2), and gastric mucosal-to-arterial CO_2 (Pgtis-aCO_2). Similarly, Nevière et al. [46] reported that variations in gastric microvascular blood flow were tracked by variations in gastric mucosal-to-arterial PCO_2 differences (Pgtis-aCO_2), suggesting that microvascular blood flow may play an important role in gastric-tissue CO_2 accumulation.

Some investigators have suggested a close link between microcirculatory blood flow derangements and Pv-aCO_2 during the early stages of septic shock [18, 47]. Increases in Pv-aCO_2 were paralleled by a gradual decrease in sublingual functional capillary density and increased microvascular flow heterogeneity, independently of cardiac output variations [18]. Likewise, Pv-aCO_2 was related to microcirculatory alterations and reduced tissue oxygenation, although this relationship was dependent on cardiac output [47]. However, in that study, microcirculation was evaluated using near-infrared spectroscopy, a technique that does not directly measure microcirculatory blood flow [47].

During severe tissue hypoxia, total VCO_2 decreases even when non-aerobic CO_2 generation is present [20, 21, 33]. Nevertheless, both low cardiac output and potentially increased heterogeneity of microvascular blood flow respond, to some extent, to the increases in venous CCO_2 [18].

What is the difference between tissue PCO_2 and venous PCO_2?

Most of the CO_2 is produced by the tissues, in aerobic as well as in hypoxic conditions. CO_2 easily diffuses to capillaries and venules so that the gradient between tissue PCO_2 and $PvCO_2$ is usually very low (2–4 mmHg). When tissue hypoxia occurs, at the point of critical DO_2, tissue PCO_2 sharply increases. Interestingly, CO_2 can diffuse longer distances than O_2, so that it can still reach the venous side in very low flow conditions, even when some areas are almost not perfused. Nevertheless, the gradient between arterial PCO_2 and tissue PCO_2 would be much higher than Pv-aCO_2. In an experimental tamponade, Schlichtig et al. have shown that tissue PCO_2 in the gastric mucosa reached levels between 90 and 210 mmHg while portal vein PCO_2 reached "only" 80 mmHg [35]. However, a locally increased PCO_2 in the gastric mucosa might not reflect hypoperfusion in the entire regional circulation. In an experimental model of sepsis, with preserved cardiac output but associated with splanchnic hypoperfusion, Ospina et al. reported that the ileal tissue-arterial PCO_2 gradient increased more than Pv-aCO_2 in the mesenteric vein [48].

Other factors influencing the PCO_2 gap

Factors related to the PCO_2:CCO_2 relationship

Pv-aCO_2 or central Pv-aCO_2 (Pcv-aCO_2), calculated as the difference between central venous PCO2 sampled from a central vein catheter and arterial PCO_2, may be influenced by factors beyond blood flow and anaerobic metabolism, as they affect the PCO_2:CCO_2 relationship. While this relationship remains quasi-linear within the physiological PCO_2 range [49], it becomes curvilinear when altered by certain conditions [26]. Key influencing factors include oxygen saturation (Haldane effect) [50, 51], the degree of metabolic acidosis [52], and hematocrit levels [51].

Haldane effect Low local hemoglobin oxygen saturation increases CCO_2 for a given PCO_2 as deoxygenated hemoglobin binds more CO_2 due to the Haldane effect (Fig. 2A) [53, 54]. In conditions of very low SvO_2 (< 30%), Jakob et al. [55] found that changes in gastric mucosal Pv-aCO_2 may not always reflect changes in CCO_2 differences or blood flow, potentially due to the Haldane effect. However, gastric mucosal oxygen saturation was not directly measured but rather estimated based on gastric mucosal oxygen extraction, which may have influenced these results. In an experimental study using a vascularly isolated, innervated, and perfused dog hindlimb, Mallat and Vallet [56] observed that the Haldane effect did not significantly influence the PCO_2:CCO_2 relationship, even when regional SvO_2 dropped well below 30%. Similarly, in healthy individuals during intense exercise, Sun et al. [57] reported that variations in SvO_2 had only a minor impact on the PCO_2:CCO_2 relationship. Additionally, in septic shock patients, Mesquida et al. [58] found that SvO_2 (Haldane effect) had a minimal impact on the PCO_2:CCO_2 relationship, further suggesting that its clinical significance may be limited.

Metabolic acidosis effect Hydrogen ions accumulation can shift the PCO_2:CCO_2 relationship so that PCO_2 is higher for a given CCO_2 (Fig. 2B). In an experimental study using a perfused dog hindlimb model [56], metabolic acidosis significantly impacted the PCO_2:CCO_2 relationship. When venous pH changes were ignored, the relationship remained nearly linear. However, when pH variations were accounted for, CCO_2 was no longer linearly related to PCO_2. As metabolic acid accumulated from hypoxic cells, PCO_2 and CCO_2 changed in opposite directions due to decreased plasma and red blood cell CCO_2 and bicarbonate levels. Similarly, during heavy exercise in healthy individuals, Sun et al. [57] found that once the lactic acidosis threshold was reached, pH changes disrupted the linearity of the PCO_2:CCO_2 relationship, with CCO_2 and PCO_2 sometimes moving in opposite directions. In patients with septic shock, Mesquida et al. [58] identified metabolic acidosis (pH) as the primary predictor of the discrepancy between mixed Pv-aCO_2/Ca-vO_2 and Cv-aCO_2/Ca-vO_2. Thus, in situations with moderate/severe metabolic acidosis, an elevated Pv-aCO_2 might not reflect only low or inadequate cardiac output but could also be ascribed to modifications of the CO_2–hemoglobin dissociation curve, suggesting the reliability of Pv-aCO_2 and its combination with O_2-derived variables as markers of tissue perfusion and cell metabolic dysfunction during shock.

Hemoglobin effect The impact of hemoglobin on the PCO_2:CCO_2 relationship has been less extensively studied. In surgical patients with sepsis and varying degrees of illness, Chiarla et al. [51] observed that a decrease in hemoglobin levels increased Pv-aCO_2 for a given CCO_2. However, this effect was minimal under normal physiological conditions and became significant only in extreme scenarios. In such cases, a combination of low hemoglobin concentration, low-flow states, acidosis, and hypercapnia may synergistically disrupt the physiological balance, amplifying the impact on the PCO_2:CCO_2 relationship, leading to a disproportionate rise in Pv-aCO_2 relative to CCO_2.

Factors related to an acute change in $PaCO_2$

Under spontaneous breathing conditions, hyperventilation triggered by reduced blood flow may decrease $PaCO_2$, thus preventing the rise in $PvCO_2$ that typically results from CO_2 stagnation [59]. This observation

highlights the advantage of evaluating the PCO_2 gap instead of relying solely on $PvCO_2$ measurements, especially when patients are breathing spontaneously [60].

However, acute changes in $PaCO_2$ due to ventilator adjustments may influence the PCO_2 gap. In a small study of 10 mechanically ventilated postoperative patients, Morel et al. [61] found that acute hyperventilation significantly increased Pcv-aCO_2 without affecting cardiac output. Similarly, in patients with septic shock, Mallat et al. [62] demonstrated that acute hyperventilation increased Pcv-aCO_2 independently of cardiac output. This rise was attributed to increased VO_2 triggered by acute respiratory alkalosis. These findings regarding the effects of hyperventilation on the Pcv-aCO_2 were later confirmed by Guo et al. [63]. Clinicians should be mindful of the impact of alveolar hyperventilation on PCO_2 gap when interpreting its values at the bedside, as it may not always reflect the perfusion status alone.

The venous-arterial PCO_2 and CO_2 content to arterial-venous O_2 content ratio (Cv-aCO_2/Ca-vO_2 and Pv-aCO_2/Ca-vO_2 ratios)

Physiological rationale

According to the Fick equation, VO_2 and VCO_2 are directly proportional to cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Under aerobic steady-state conditions, VCO_2 approaches VO_2, whereby the mixed venous-to-arterial CCO_2 (Cv-aCO_2) approximates to the arterial-to-mixed-venous O_2 content difference (Ca-vO_2). VCO_2 should not exceed O_2 availability, and consequently, the VCO_2/VO_2 ratio should not be > 1.0 under normal metabolic steady-state conditions. In these terms, the Cv-aCO_2/Ca-vO_2 ratio could represent some approximation of the VCO_2/VO_2 ratio or RQ, and it should be independent of blood flow variations as the cardiac output is present in both the numerator and denominator components [16, 52].

Experimental blockade of mitochondrial O_2 utilization leads to non-symmetrical reductions in VCO_2 and VO_2, with the subsequent increase in the RQ [22]. Other experimental shock models induced by central hypovolemia also showed that VCO_2 decreased less than the VO_2 decrease, with the subsequent increase in the VCO_2/VO_2 ratio [21]. An asymmetric fall in VCO_2 and VO_2 could be explained by increased non-aerobic VCO_2 as a result of buffering of excess H^+ due to severely limited tissue O_2 availability (tissue hypoxia), or alternatively, because of mitochondrial dysfunction. Interestingly, the VCO_2/VO_2 ratio returns to normal after shock resolution, such as seen in the splanchnic regional Cv-aCO_2/Ca-vO_2 ratio after resuscitation in experimental peritonitis models [48] and endotoxemic shock [64]. Other authors have also observed simultaneous increases in the Cv-aCO_2/Ca-vO_2 ratio, RQ, and lactate levels during circulatory failure in mechanically ventilated patients [65, 66], thus reinforcing the idea of a link between non-aerobic VCO_2 and increased Cv-aCO_2/Ca-vO_2 ratio. Contrastingly, a sub-analysis of an experimental model of progressive hemorrhage suggested that the Pv-aCO_2/Ca-vO_2 ratio is a poor surrogate of anaerobic metabolism during marked hemodilution [50]. Nevertheless, at extremely low hemoglobin levels (~ 2 g/dL, rarely seen in clinical practice), inherent measurement errors may be amplified in the total Pv-aCO_2/Ca-vO_2 ratio. In such conditions, indirect calorimetry may also be inappropriate due to the highly variable time required for equilibration among different CO_2 stores (CO_2 dissolved in plasma, bicarbonate, and tissue CO_2) during the induction and resuscitation of shock. Furthermore, PCO_2 can rise sharply at very low hematocrit levels, with minimal changes in total CCO_2, because reduced hemoglobin impairs CO_2 buffering and binding capacity [51].

In conclusion, the Cv-aCO_2/Ca-vO_2 ratio and its potential equivalent, the Pv-aCO_2/Ca-vO_2 ratio, could identify the presence of non-aerobic VCO_2, whether mediated by tissue hypoxia (limited O_2 availability) or mitochondrial dysfunction (with preserved O_2 availability) (Fig. 1).

Clinical relevance of PCO_2 gaps

Septic shock High $ScvO_2$ does not exclude the presence of tissue hypoperfusion and hypoxia in cases of impaired oxygen extraction, which can occur in septic shock [67, 68]. Due to its high solubility—approximately 20 times that of oxygen—CO_2 readily diffuses from ischemic tissues into efferent veins, making it a highly sensitive marker of hypoperfusion. As a result, in conditions where oxygen diffusion is impaired due to shunted or obstructed capillaries, the PCO_2 gap can help to reveal underlying hypoperfusion.

In a prospective study that included 64 patients with septic shock, non-survivors had a significantly higher Pv-aCO_2 than survivors (5.9 ± 3.4 mm Hg vs. 4.4 ± 2.3 mm Hg, $p < 0.05$), related to a higher $PvCO_2$ level. Furthermore, patients with an increased Pv-aCO_2 (≥ 6 mmHg) were more likely to die (73.3% vs. 32.6%, $p < 0.01$) [39]. Also, Ospina-Tascón et al. [15] demonstrated that persistently elevated Pv-aCO_2 (≥ 6 mmHg) after the first six hours of resuscitation in patients with septic shock was associated with more severe multiple organ failure and higher mortality rates. However, measuring mixed Pv-aCO_2 requires a pulmonary artery catheter, which is more rarely used in current clinical practice [69]. Since most patients with septic shock have a central venous catheter in place, central Pv-aCO_2 (Pcv-aCO_2) offers a more practical alternative with comparable clinical utility. Interestingly, a strong agreement between Pv-aCO_2 and Pcv-aCO_2, was reported in critically ill patients [70]

and in patients with severe sepsis or septic shock [42]. However, in septic patients, the 95% limits of agreement were wide, suggesting that while both mixed and central venous PCO_2 can be used to calculate the PCO_2 gaps, they should not be used interchangeably during treatment.

While reduced oxygen extraction and increased tissue oxygen debt may mask hypoxia, CO_2 continues to diffuse into the efferent veins, exposing the hypoperfusion state to clinicians when Pcv-aCO_2 is assessed [71]. Vallée et al. [14] tested the hypothesis that Pcv-aCO_2 could serve as a global indicator of tissue hypoperfusion in resuscitated septic shock patients with $ScvO_2 > 70\%$. They found that despite normalizing the DO_2/VO_2 ratio, patients with persistent tissue hypoperfusion, indicated by blood lactate concentrations > 2 mmol/L, also exhibited elevated Pcv-aCO_2 (> 6 mmHg). Moreover, patients with lower Pcv-aO_2 values showed larger reductions in blood lactate concentrations, higher cardiac output values, and significantly larger decreases in SOFA scores than those with persistently high Pcv-aCO_2. In a prospective study of 80 patients, Mallat et al. assessed the clinical value of measuring Pcv-aCO_2 during the early resuscitation phase of septic shock [72]. The findings revealed that patients who achieved a normal Pcv-aCO_2 (≤ 6 mmHg) within six hours of resuscitation experienced greater decreases in blood lactate concentrations and SOFA scores than those who did not [72]. Notably, patients who met both Pcv-$aCO_2 \leq 6$ mmHg and $ScvO_2 > 70\%$ targets within the first six hours had the most significant reductions in blood lactate concentrations, which emerged as an independent prognostic factor for ICU mortality [72].

Supporting these findings, Du et al. [73] conducted a retrospective study showing that the simultaneous achievement of $ScvO_2$ normalization and central Pcv-$aCO_2 \leq 6$ mmHg was a stronger predictor of favorable outcomes after septic shock resuscitation than $ScvO_2$ alone, as blood lactate was cleared more effectively in patients meeting both targets. Wang et al. [74] reported in a prospective study of 152 septic shock patients that Pcv-aO_2 was independently associated with 28-day mortality in a multivariable regression analysis. Other prospective studies found a significant association between Pcv-aCO_2 and mortality in patients with sepsis or septic shock [75–78].

An important question is whether PCO_2 gap can serve as a target for resuscitation. In a recent randomized controlled trial (RCT) that included 179 patients with acute circulatory failure who were assigned to receive either a CO_2-O_2-derived algorithm-based treatment or standard of care clinical practice for hemodynamic resuscitation, there was no significant difference between the two groups regarding the primary outcome, which was lactate clearance > 10% at two hours. Additionally, the secondary outcomes (SOFA score, ICU and hospital length of stay, and 28-day mortality) did not show significant differences between the two groups [79]. Further trials are needed to assess the effectiveness of targeting Pcv-aCO_2 as the end-goal of hemodynamic resuscitation in septic shock patients. Importantly, one should recall that PCO_2 gaps, as lactate, should not be looked at in isolation [80]. PCO_2 gaps, lactate, capillary refill time, and other indices of tissue hypoperfusion should be integrated, and attempts to continue resuscitation may be paused when the majority of indices are normalized.

Major non-cardiac surgery Robin et al. [81] conducted a prospective study including 115 high-risk non-cardiac surgery patients, primarily undergoing abdominal surgery. They reported that Pcv-aCO_2 measured upon ICU admission was significantly higher in patients who developed postoperative complications than those who did not (8.7 ± 2.8 mmHg vs. 5.1 ± 2.6 mmHg, $p = 0.001$). Additionally, Pcv-aCO_2 on ICU admission predicted postoperative complications with an AUROC of 0.86, with an optimal cutoff value of 5.8 mmHg. Notably, Pcv-aO_2 was a superior predictor of postoperative complications compared to arterial lactate concentrations. A higher than normal Pcv-aCO_2 (≥ 6 mmHg) was associated with increased organ failure, prolonged mechanical ventilation, and extended hospital stay. Several observational studies have identified an association between Pcv-aCO_2 and outcomes in high-risk non-cardiac surgical patients [82–84]. However, an RCT of 100 patients undergoing major surgery found that goal-directed therapy to maintain Pcv-$aCO_2 < 6$ mmHg did not improve organ function compared to a standard approach [85]. Nevertheless, it led to increased dobutamine use, improved tissue oxygenation parameters, and a reduced ICU length of stay [85]. Additionally, a prospective cohort study found no association between Pcv-aCO_2 and survival or postoperative adverse outcomes in critically ill patients following liver transplantation [86]. While the overall findings are promising, further evidence is needed to support the routine use of Pcv-aCO_2 as a hemodynamic resuscitation target in major non-cardiac surgery patients.

Cardiac surgery Clinical studies have reported conflicting findings regarding Pcv-aCO_2 in cardiac surgery patients [87–96]. Indeed, in a prospective study of 110 cardiac surgery patients with cardiopulmonary bypass (CPB), Mukai et al. reported that postoperative Pv-aCO_2 was independently associated with major organ morbidity and mortality (MOMM) and was the strongest predictor of MOMM, with an AUROC of 0.80 and a cut-off value of 5.2 mmHg [87]. Similarly, other observational studies have found that Pv-aCO_2 predicted postoperative compli-

cations and was independently associated with ICU mortality [88–91].

In contrast, some studies have reported a limited ability of Pcv-aCO_2 to predict outcomes in cardiac surgery patients [92–96]. Indeed, a retrospective study of 220 patients undergoing cardiac surgery with CPB found that Pcv-aO_2 had poor predictive value for postoperative outcomes [92]. A recent retrospective study of 1,933 patients further confirmed the poor diagnostic performance of Pcv-aCO_2 in predicting postoperative complications (AUROC = 0.55), despite its independent association with adverse outcomes [93]. Similarly, other observational studies have reported that Pcv-aCO_2 did not predict major postoperative complications and was not a reliable indicator of organ dysfunction in cardiac surgery patients undergoing CPB [94–96]. These negative findings may be attributed to the effects of CPB on Pcv-aCO_2. Indeed, CPB influences CO_2 production, hemoglobin dilution, and pH changes, potentially altering the PCO_2:CCO_2 relationship. Additionally, hypothermia during surgery and subsequent rewarming can impact VCO_2 and further affect the relationship between PCO_2 gaps and major postoperative complications [97]. After myocardial revascularization, Pv-aCO_2 was found to be a nonspecific parameter influenced primarily by VO_2, body temperature, and $PaCO_2$ rather than tissue perfusion [98].

A meta-analysis of 21 studies (n = 2,155 patients) across medical (n = 925), cardiovascular (n = 685), surgical (n = 483), and mixed (n = 62) ICUs found that elevated Pcv-aCO_2 was associated with higher blood lactate concentrations, lower cardiac output, and reduced $ScvO_2$. Additionally, in patients with shock, a high Pcv-aCO_2 was linked to increased mortality (OR = 2.22, p = 0.004), but only in medical and major non-cardiac surgical patients [99]. No significant association was found between Pcv-aCO_2 and outcomes in cardiac surgery patients. However, the meta-analysis included only two studies on cardiac surgery, making these negative findings inconclusive. As a result, the relationship between Pcv-aCO_2 or Pv-aCO_2 and outcomes in cardiac surgery patients remains unclear. Further studies are needed to refine its prognostic value and establish its role in clinical practice.

Assessment of oxygen supply to demand adequacy: effects of Dobutamine Dobutamine, a synthetic catecholamine with strong inotropic effects due to its predominant β1-adrenergic properties [100], is commonly used to increase cardiac output and ensure adequate DO_2 to meet tissue demands. However, beyond its systemic hemodynamic effects, dobutamine can also increase VO_2 and VCO_2 through its direct cellular metabolic stimulation [34, 101].

Two studies examined the effects of dobutamine titration (0 to 15 µg/kg/min) in patients with septic shock [102] and in patients with stable congestive heart failure [34]. Both studies reported a dose-dependent increase in cardiac output and DO_2, with distinct responses at different dosage ranges [34, 102].

Between 0 and 10 µg/kg/min, dobutamine increased cardiac output and DO_2 dose-dependently. The VCO_2 increased, but much less than the cardiac output. This explains the commensurate decrease in Pcv-aCO_2 attributed to increased blood flow and improved CO_2 washout. As anticipated, SvO_2 and $ScvO_2$ improved as DO_2 increased to organs that were still in need of oxygen. At these doses, dobutamine primarily enhances hemodynamics, improves organ perfusion, and facilitates CO_2 clearance [34, 102]. At higher doses (10–15 µg/kg/min), while cardiac output continued to increase, VCO_2 rose proportionally, leading to a stable Pcv-aCO_2. This plateau effect is attributed to dobutamine's β-adrenergic stimulation, which directly increases cellular metabolism, oxygen consumption, and CO_2 production—a thermogenic effect observed only at these higher doses [34, 102].

Thus, Pcv-aCO_2 (or Pv-aCO_2) may reflect dobutamine-induced changes in VCO_2 and help distinguish between its hemodynamic and metabolic effects in critically ill patients [103]. Given its ease of bedside measurement and its complementary value alongside other tissue perfusion markers, Pcv-aCO_2 could serve as a useful tool for guiding hemodynamic management in the ICU.

Response to fluids In a recent post-hoc analysis of a multicenter prospective study, Mallat et al. examined 205 mechanically ventilated patients with acute circulatory failure [104]. Fluid responsiveness was defined as an increase in cardiac index of > 15% following fluid administration. A post-fluid challenge decrease in Pcv-aCO_2 ≤ 2.1 mmHg and an increase in $ScvO_2$ ≥ 3.4% effectively differentiated fluid responders from fluid non-responders, with positive predictive values of 90% and 86% and negative predictive values of 58% and 64%, respectively. Additionally, both ΔPcv-aCO_2 and Δ$ScvO_2$ were independently associated with fluid responsiveness in multivariable analysis. Notably, no significant relationships were found between pre-infusion $ScvO_2$ or Pcv-aO_2 levels and fluid responsiveness, which is in agreement with previous findings [105]. These findings suggest that if Pcv-aCO_2 decreases by > 2 mmHg after a fluid challenge, clinicians can be fairly confident that the patient has responded to the fluid administration. However, if ΔPcv-aCO_2 remains unchanged, fluid responsiveness cannot be ruled out, particularly in patients with tissue hypoxia due to the VO_2/DO_2 dependency phenomenon [106, 107].

Moreover, the negative predictive value of Δ$ScvO_2$ was poor, meaning it cannot reliably rule out the presence of fluid responsiveness [104]. Several factors may explain this limitation. Fluid administration can cause

hemodilution, leading to a decrease in hemoglobin concentrations and arterial oxygen content, potentially blunting increases in $ScvO_2$ [108]. Additionally, in states of VO_2/DO_2 dependency, an increase in cardiac output following fluid administration may also lead to a rise in VO_2, as the body repays its oxygen debt—thereby limiting the increase in $ScvO_2$ [106, 107]. However, despite its limitations in ruling out fluid responsiveness, $\Delta ScvO_2$ demonstrated a strong positive predictive value for confirming the presence of fluid responsiveness [104]. These findings align with a recent meta-analysis of five observational studies involving 240 critically ill patients, further supporting its clinical utility [109].

In summary, while variations in $Pcv\text{-}aCO_2$ and $ScvO_2$ may serve as markers of fluid responsiveness in selected cases, their interpretation is limited in the presence of tissue hypoxia.

Weaning from mechanical ventilation Weaning is typically associated with an increase in VO_2 due to the higher work of breathing [110, 111]. An appropriate increase in cardiac output and DO_2 is required to meet this increased metabolic demand, which may justify the use of markers of the adequacy of cardiac output to oxygen demand. Indeed, several studies have shown that a decrease in SvO_2 during a spontaneous breathing trial (SBT) was associated with weaning and extubation failure [112, 113]. In one study, SvO_2 progressively declined in patients who failed SBT but remained stable in those who succeeded [112]. This drop was attributed to increased oxygen extraction, likely due to the increased activity of the respiratory muscles. Similarly, Teixeira et al. [113] found that changes in $ScvO_2$ from mechanical ventilation to the end of SBT were independently associated with extubation failure in patients with weaning difficulty. A decline in $ScvO_2 > 4.5\%$ predicted extubation failure with a high positive predictive value of 93% and a negative predictive value of 90%.

Mallat et al. conducted a prospective multicenter study to assess the usefulness of this metabolic approach in predicting weaning outcomes from mechanical ventilation [114]. The study enrolled 75 patients, with extubation failure occurring in 24%. Changes in $Pcv\text{-}aCO_2$ ($\Delta Pcv\text{-}aCO_2$) and $ScvO_2$ ($\Delta ScvO_2$) during an SBT demonstrated a strong predictive value for extubation outcomes, with AUROCs of 0.865 and 0.856, respectively. However, combining $\Delta ScvO_2$ and $\Delta Pcv\text{-}aCO_2$ significantly improved the detection of extubation failure, yielding an AUROC of 0.940, which was superior to $\Delta ScvO_2$ alone ($p = 0.04$) and $\Delta Pcv\text{-}aCO_2$ alone ($p = 0.03$). Additionally, both $\Delta Pcv\text{-}aCO_2$ and $\Delta ScvO_2$ were independently associated with extubation failure (OR = 1.02; $p = 0.006$, and OR = 0.84; $p = 0.02$, respectively).

The $Cv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratios and their clinical implications

Hyperlactatemia has traditionally been recognized as a marker of anaerobic metabolism secondary to inadequate cell oxygen supply [115]. In this regard, Mekontso-Dessap et al. [16] showed a significant association between the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio and blood lactate concentrations ≥ 2.0 mmol/L, but not between blood lactate concentrations and isolated $Pv\text{-}aCO_2$ or $Cv\text{-}aCO_2$ values. Nevertheless, blood lactate concentrations may increase due to many other causes than tissue hypoxia [116–118]. Remarkably, the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio (or its potential equivalent, the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio) could provide additional information to blood lactate concentrations, as non-aerobic VCO_2 reflects abnormal cellular metabolism. Indeed, the combination of high $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio and high blood lactate concentrations during the very early stages of resuscitation in septic shock was associated with more severe organ dysfunction and worse clinical outcomes when compared with patients attaining normal blood lactate concentrations and $Cv\text{-}aCO_2/Ca\text{-}vO_2 \leq 1.0$ [17]. Remarkably, persistently high $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratios were related to more severe organ dysfunction and worse clinical outcomes even in patients who simultaneously attained normal blood lactate concentrations [17]. $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio should react faster than blood lactate concentrations to short-term hemodynamic changes [13]. This makes this ratio an attractive variable to monitor, and although it is a little difficult to calculate, its interpretation is easier, with values > 1.0, suggesting ongoing anaerobic CO_2 generation as a consequence of tissue acidosis. Thus, a high $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio should reflect non-aerobic CO_2 generated as a consequence of buffering of the excess of H^+ (most of them coming from ATP hydrolysis) not recycled in the normal cell energy-generating processes (Fig. 1).

Subsequent studies corroborated the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio as a prognostic factor in humans with septic shock [119–121] and its relationship with regional lactate/pyruvate ratio and acute kidney injury in experimental models [122]. In addition, increases in VO_2 following fluid loading were better predicted by both $Ccv\text{-}aCO_2/Ca\text{-}cvO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ ratios than by blood lactate concentrations [107] or by baseline $ScvO_2$ [106], which suggests the superiority of $Ccv\text{-}aCO_2/Ca\text{-}cvO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ ratios over O_2-derived variables and lactate kinetics to detect tissue hypoxia or to some extent, to detect non-aerobic VCO_2. Furthermore, experimental data suggest that restoration of microcirculatory blood flow distribution parallels proportional normalization in the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio in septic shock [48, 64].

Despite the apparent equivalence between $Cv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratios, conflicting results have been reported, as some authors showed that

$Cv\text{-}aCO_2/Ca\text{-}vO_2$ but not $Pv\text{-}aCO_2/Ca\text{-}vO_2$ was related to adverse clinical outcomes in septic shock [17]. In contrast, others demonstrated that only $Pv\text{-}aCO_2/Ca\text{-}vO_2$ did [58]. This may be attributed to the complex nature of the PCO_2:CCO_2 relationship, which is influenced by multiple physiological factors (see limitations of $Pv\text{-}aCO_2$ section).

In conclusion, high $Cv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratios might reflect increased non-aerobic VCO_2 generation during tissue hypoxia or even under normoxic conditions, but with concomitant cell acidosis.

Errors in PCO_2 gap calculation

Several pre-analytical sources of error in PCO_2 measurement must be minimized to ensure accurate interpretation of $Pv\text{-}aCO_2$. These include using inappropriate sample containers, insufficient sample volume relative to the anticoagulant, and contamination from resident fluid in the line, air bubbles, or venous blood. Even with strict precautions to reduce pre-analytical and analytical errors, a prospective study by Mallat et al. [123] found that the least significant change (the minimal change required to confirm a true measurement variation) for $Pcv\text{-}aCO_2$ was ± 2 mmHg. This implies that changes in $Pcv\text{-}aCO_2$ must exceed ± 2 mmHg to be considered clinically significant rather than a result of natural measurement variability [123].

Overall, clinicians should remain aware of these limitations, but these factors should not discourage the clinical use of $Pv\text{-}aCO_2$.

Conclusions

Tissue hypoxia occurs when cells exhibit abnormal oxygen utilization, triggering anaerobic metabolism. Early identification of tissue hypoperfusion and hypoxia is critical to preventing clinical deterioration. Various tools are available for detecting and monitoring these conditions, but many require specialized equipment that is either unavailable in most ICUs or primarily used for research purposes. Based on CO_2- and O_2-derived variables, the metabolic approach offers an attractive alternative, as it only requires a central venous catheter and an arterial line—devices already in place for most critically ill patients. Numerous experimental and clinical observational studies have demonstrated the reliability of $Pcv\text{-}aCO_2$ and the $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ ratio in detecting tissue hypoperfusion and the presence of anaerobic metabolism (tissue hypoxia), respectively, particularly in

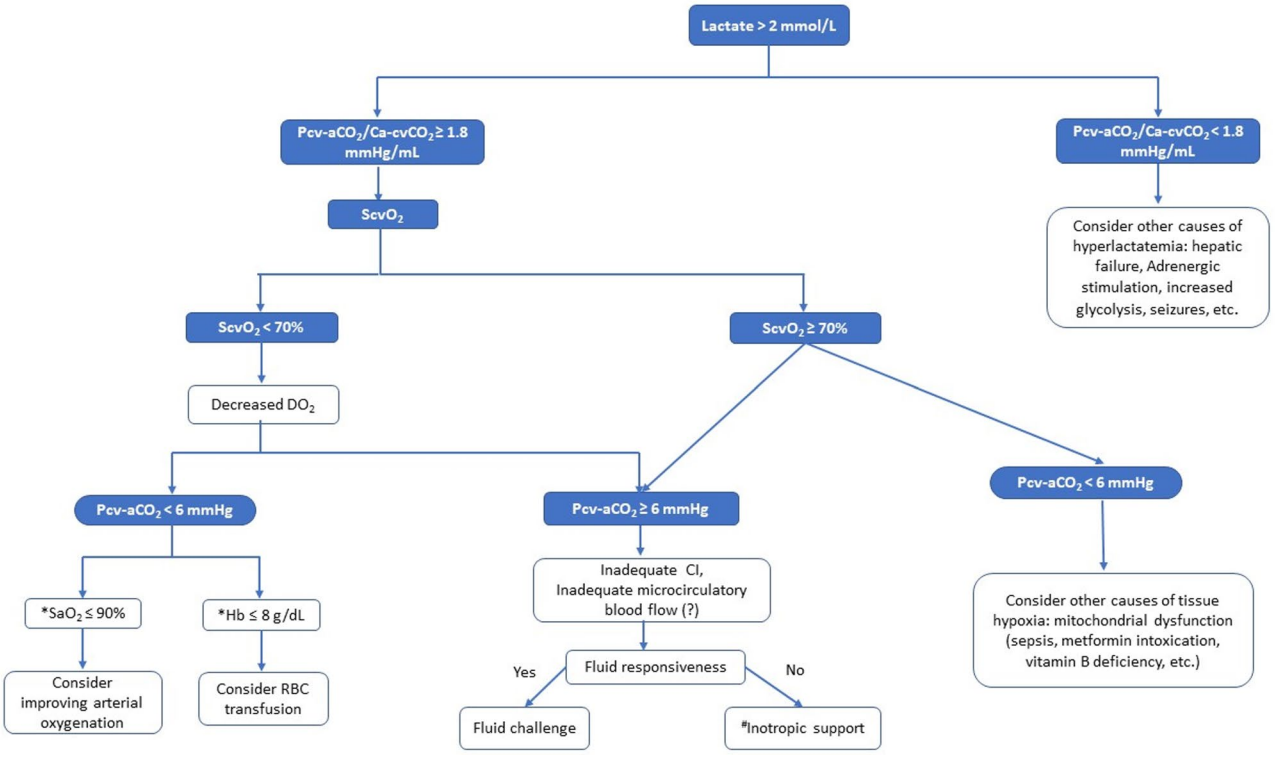
Lactate > 2 mmol/L
Pcv-aCO2/Ca-cvCO2 ≥ 1.8 mmHg/mL
Pcv-aCO2/Ca-cvCO2 < 1.8 mmHg/mL
ScvO2
Consider other causes of hyperlactatemia: hepatic failure, Adrenergic stimulation, increased glycolysis, seizures, etc.
ScvO2 < 70%
ScvO2 ≥ 70%
Decreased DO2
Pcv-aCO2 < 6 mmHg
Pcv-aCO2 ≥ 6 mmHg
Pcv-aCO2 < 6 mmHg
*SaO2 ≤ 90%
*Hb ≤ 8 g/dL
Inadequate CI, Inadequate microcirculatory blood flow (?)
Consider other causes of tissue hypoxia: mitochondrial dysfunction (sepsis, metformin intoxication, vitamin B deficiency, etc.)
Consider improving arterial oxygenation
Consider RBC transfusion
Yes
Fluid responsiveness
No
Fluid challenge
#Inotropic support

Fig. 3 CO_2 and O_2-derived variables guided protocol. Proposed guided algorithm integrating lactate, central venous oxygen saturation ($ScvO_2$), the central venous-to-arterial CO_2 pressure difference ($Pcv\text{-}aCO_2$), and the ratio between $Pcv\text{-}aCO_2$ and the difference between arterial and central venous oxygen content ($Pcv\text{-}aCO_2/Ca\text{-}cvO_2$). SaO_2, arterial oxygen saturation; CI, cardiac index; Hb, hemoglobin; RBC, red blood cell

* $SaO_2 \leq 90\%$ and Hb ≤ 8 g/dL are provided as general references and should be interpreted in the context of the clinical situation

We advise performing echocardiography before considering inotropic support

septic shock and in postoperative non-cardiac surgery patients. Furthermore, these markers have been associated with clinical outcomes. Several diagnostic algorithms incorporating Pv-aCO_2 have been proposed, as shown in Fig. 3. However, multicenter RCTs are needed to validate the efficacy of the metabolic approach compared to standard hemodynamic management strategies in patients with acute circulatory failure.

Abbreviations

CO_2	Carbon dioxide
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption
$PvCO_2$	Venous carbon dioxide partial pressure
$PaCO_2$	Arterial carbon dioxide partial pressure
RQ	Respiratory quotient
HCO_3^-	Bicarbonate
H_2CO_3	Carbonic acid
H_2O	Water
DO_2	Oxygen delivery
ATP	Adenosine triphosphate
H^+	Hydrogen ion
CO_3^{2-}	Carbonate
Cl^-	Chloride anion
OH^-	Hydroxide anion
R-NH_2	Amino groups
Hb-NH-COO^-	Carbamino hemoglobin
CCO_2	Carbon dioxide content
O_2	Oxygen
PO_2	Partial pressure of oxygen
Cv-aCO_2	Venous to arterial carbon dioxide content difference
Ca-vO_2	Arterial to venous oxygen content difference
Pv-aCO_2	Venous-to-arterial carbon dioxide pressure difference
$CvCO_2$	Venous carbon dioxide content
$CaCO_2$	Arterial carbon dioxide content
FCD	Functional capillary density
Psl-aCO_2	Sublingual-to-arterial CO_2 partial pressure difference
Pmtis-aCO_2	Gut mucosal-to-arterial PCO_2 difference
Pgtis-aCO_2	Gastric mucosal-to-arterial PCO_2 differences
$ScvO_2$	Central venous oxygen saturation
SvO_2	Mixed venous oxygen saturation
OR	Odds ratio
RCT	Randomized controlled trial
ICU	Intensive care unit
SOFA	Sequential organ failure
AUROC	Area under the receiver operating curve
MOMM	Major organ morbidity and mortality
CPB	Cardiopulmonary bypass
SBT	Spontaneous breathing trial

Supplementary Information

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Supplementary Material 1.

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JM and GOT conceived and designed the review, prepared the initial draft, and finalized the manuscript. MJ, OH, XM, JLT, NO, and DDB contributed to the conceptualization of the main ideas and critically reviewed the manuscript and provided critical feedback on the final draft. All authors have read and approved the final version of the manuscript.

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